

at least a one year time span after first administration, on the incidence of a chronic immune-mediated disorder when administered to humans in accordance with at least one immunization schedule, and

- (b) labeling said human vaccine with labeling indicating that said human vaccine may affect the incidence of said chronic-immune-mediated disorder.

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Claims 78, 79, 81, 83, 84, and 85 are 26-way dependent, and claims 80 and 82 are dependent on 26-way dependent claims. Hence, these 8 claims count as $8 \times 26 = 208$ total claims.

Claim 119 is 6-way dependent and claim 124 is 30-way dependent.

So the effective total claims for fee calculation purposes = $103 + 208 + 6 + 30 = 347$ total claims.

There are 10 independent claims.

1. General Remarks

1.1. An Appeal Brief was filed in this case on May 1, 2000. Instead of filing an Examiner's Answer, the Examiner reopened prosecution. In the action it appears that the Examiner believes that the last claim added was 101. However, a Substitute Supplemental After Final Rejection was filed on May 1, 2000, adding claims 102-105. (This amendment is referred to in section 1.4 of Appellant's Brief). The May 1 amendment should have been entered as a matter of right when prosecution was reopened. Since claims 102-106 were not considered, the June 20, 2000 action is incomplete. The Examiner should either issue a supplemental action, or make the next action nonfinal.

In view of the complexity of the past and present rejections, we summarize the current issues below, with new issues boldfaced. (For old issues, the roman numerals refer to the issues presented in our Appeal Brief.)

Definiteness (OA \$5)

-**antecedent basis (claims 6, 57, 11, 38)**

-**"substantially"** (claims 6, 27) (II, III)

-**immunogen identified by disease name rather than etiologic agent (claim 19)**

-**"herpes"** (claim 19)

-**cross-reacting immunogen (claim 19)**

-**"less than 28 days"** inconsistent with base claim

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(claim 40)

- "animal model" of diabetes or SLE (claim 48)**
- improper Markush format (claim 77)**

Description/New Matter (OA §6)

- at least one immunogen other than BCG (claim 32) (VI)**
- prior art pertussis schedule exclusion (claim 32) (VI)**
- >4 dates in first 42d (claim 58)**
- label warning of possible bad effect (claim 59(b))**
- adjuvant equivalent in Al salt (claim 89)**

Enablement (OA §7)

- relies on Pediatric Infectious Diseases Journal, 18:217-22 (1999) as teaching that it is inconclusive whether vaccines can protect against or increase the risk of diabetes (see p. 9)**
- relies on Boumpas for teaching that underlying pathogenesis of SLE is largely unknown extremely complex, and different in different patients (X)**
- PIDJ says that vaccines are protective against type 1 diabetes in mice, but not humans (or at least inconclusive therein)**
- therefore, improper to extrapolate from mice to humans (VIII)**
- disclosure does not teach how immunization protocol is to be adapted for autoimmune diseases other than SLE (X; see also XI)**

Double Patenting (OA §8) (not a significant issue)

Prior Art (OA §9)

- anticipation by Madore (§ab) (I)**
- anticipation by Dengrove (§9c) (I)**

- anticipation by Halsey (§9d) (I)
- anticipation by John (§9e) (I)
- anticipation by Benveniste (§9f)**
- anticipation by Bach (§9f)**

It appears that Appeal Brief issues IV, V and IX have gone away. Issue XI (finding an effective schedule) is, to some degree, merged into issues VIII (animal →human) and X (diabetes →other disorders). Moreover, these issues, as well as VII, are subsumed in the new, more general issue, of whether the invention works at all (the "PIDJ" issue).

1.2. The Examiner says that the nomenclature used to recite the immunogens is inconsistent in that in some instances the claim recites a disease name and in other instances it recites an etiologic agent. The objection to this nomenclature as "informal" is respectfully traversed.

When only a particular etiologic agent is recited, it is applicant's deliberate intent to cover only immunogens associated with the etiologic agent. However, where a "disease name" is recited, it is applicant's deliberate intent to cover any immunogen of any etiologic agent which causes that disease. Certain diseases have multiple causes. For example, meningitis may be caused by any of the following organisms: hemophilus, pneumococcus, and meningococcus.

Hence, to recite the immunogen solely by the name of the etiologic agent, as suggested by the examiner, would defeat applicant's intent. Since the form of the claim is necessary to effectuate applicant's substantive intent, the objection is improper.

The examiner alternatively suggests adding the term "vaccines" after the list of disease names. However, the claims in question are further identifying the immunogen of the base claim, not the vaccine of the base claim. Moreover, the base

claims do not require protection against an infectious disease and the term "vaccines" could be interpreted as implying that such protection occurs.

While bacterial names are systematically identified in biological literature by genus-species, in the literature on clinical immunology it is routine to refer to an immunogen as, e.g., a "pertussis" immunogen instead of an immunogen of *Bordetella pertussis*. The present claim language is thus consistent with both the specification and with customary clinical usage. For the same reason, we decline to replace "varicella" with --varicella zoster virus--.

We have reviewed and corrected the punctuation of the claims.

1.3. In claims 35 and 85, the spelling of "erythematosus" has been corrected. The syntax of claim 37 has also been corrected.

1.4. The action is incomplete in several respects:

- (1) it did not enter the September 7, 1999 Supplemental Amendment After Final Rejection, although such amendment(s) should have been entered as of right when prosecution was reopened.
- (2) it was not responsive to Applicant's Brief filed May 1, 2000, and indeed woodenly repeated many rejections previously addressed in that Brief.

2. Definiteness

2.1. The Examiner questions the antecedent basis for claims 6, 57, 11 and 38. In claims 6, 57 and 38, the questioned language is "during the first 112 days after birth". Claim 11 refers to "during the first 175 days from birth".

Base claim 32 recites administering one or more doses of

each of one or more immunogens according to an immunization schedule. While the claim says that the first dose of the schedule must be administered when the mammal is less than 42 days old, measured from birth, it does not require that all immunizations be given before that time.

We realize that in dependent claims, one normally cannot recite "the X" unless "a/an X" has already been recited. However, to apply that rule to "during the first 112 days after birth" seems frivolous. Should we amend claim 32 to recite "during a period which is from birth to a time 112 days after birth"? Or, "where the animal is alive 112 days after birth, where during the first 112 days after birth"? Or is the Examiner looking for something else?

Similar comments apply to the other claims.

2.2. Re "substantially greater" in claim 6, please see §6.2 in the Applicant's Brief. Re "substantially reduce" in claim 27, please see §6.1 in the Applicant's Brief.

2.3. With respect to "less than 28 days" (claim 40) the law does not require that a claim with a range limitation fix the lower end of the range. As a practical matter, the interval cannot be less than one day (see definition of dose at spec., page 26, lines 8-11).

2.4. Claim 19 has been rejected as indefinite "for recitation of immunogens by the disease name, rather than by the name of the etiologic agent, for those diseases which may be caused by any of a plurality of agents, such as encephalitis and pneumonia, for example?"

However, a person skilled in the art can readily determine whether an immunogen is associated with a particular disease just as such a person can determine whether a particular etiologic agent is causative of a particular disease. Hence while defining the immunogen by the associated disease is in some cases broader than defining it by the etiologic agent, it is not indefinite.

2.5. In claim 19, the term "herpes" refers to any immunogen of any herpesvirus, human or animal. We are attempting to elicit a relatively nonspecific immune response and hence it is not necessary, in treating a human, that a human immunogen be used. The human body is capable of responding to animal immunogens, too, and even if such immunogens do not elicit a response protective against the cognate human infectious disease they may still elicit a response which mediates the development of a chronic immune-mediated disorder.

2.6. With regard to the meaning of "molecule that cross-reacts immunologically to at least one of said immunogens" (claim 19), since the referent immunogens are not required to elicit a protective immune response, the cross-reactive molecule can hardly be required to do so.

2.7. The art would understand the term "animal model of diabetes or SLE" (claim 48) to be an animal exhibiting sufficient characteristics of the human disease to be useful in screening. The specification expressly discloses that NOD mice and BB rats are animal models of diabetes, and that MRL/Mpj-lpr mice (Ex. 5) are useful as models of SLE. This provides a standard.

2.8. Claim 77 has been rewritten in Markush form.

3. Double Patenting (OA \$8)

Once patentability has been resolved, Applicants will submit a terminal disclaimer.

4. Prior Art (OA \$9)

4.1. With respect to anticipation by Madore, Dengrove, Halsey and John, we incorporate by reference section 5.1 (pp. 6-17) of Applicant's Brief.

However, we like to call to the Examiner several additional patents with labeling limitations, namely USP 6,102,706 ("information"), USP 4,811,845 ("indicia"), 4,828,498 ("labeling");

"cards"), and 4,689,019 (same).

4.2. With respect to anticipation by Benveniste and Lagrange, or by Bach, these references merely disclose immunogens which elicit an immune response, and do not disclose or suggest that they have the effect set forth in the "labeling" limitation of the rejected claims. Hence, the rejection is improper for the reasons set forth in §4.1 above.

5. Description (OA §6)

5.1. With respect to "at least one immunogen other than BCG", and the whole cell pertussis schedule limitations (claim 32), see section 7 of Applicant's Brief.

5.2. The rejection of claim 58 is moot as that claim has been cancelled.

5.3. Basis for a label warning of a possible bad effect (para. (b) of claim 59) resides in the recitation of a kit at pp. 51-52 (which are required by law to have labeling warning of possible adverse effects) and the discussion of warnings at page 7, lines 11-14:

The lack of concern over the ability of vaccines to induce a chronic immune mediated disorder (e.g., but not limited to, diabetes) is further evidenced by the lack of warnings on package inserts and labels of such products about such diseases.

Since the specification warns that vaccines can induce a CIMD, it follows that warnings should be provided.

Furthermore, at page 54, lines 14-21, the specification states

Alternatively, a screening trial may be designed to determine if an immunization schedule, such as a standard schedule known in the art, will induce and/or enhance the incidence and/or severity of at least one chronic immune mediated disorder. In the latter case, it may be especially useful in screening production lots of approved

vaccines for the hitherto unrecognized safety problem of inducing or exacerbating a chronic immune-mediated disorder.

If such induction or enhancement is detected, and the vaccine is still sold with labeling calling for the schedule in question, the law would require a warning. The Code of Federal Regulations is cited at page 42, line, and page 46, lines 24-25, and hence incorporated by reference at page 99, lines 22 to page 100, line 2. The CFR cites the Federal Food, Drug and Cosmetic Act, and hence the latter is also incorporated by reference, see page 99, line 27 to page 100, line 2. We can, of course, amend the specification to explicitly insert relevant portions of the CFR or FDCA into the specification, without adding "new matter".

5.4. The basis for the use of adjuvants at least as effective as Al salt (claim 89) is in part at page 45, line 24 ("suitable adjuvants"), page 45, lines 1-6 (recitation of various depot adjuvants including Al salts). At page 75, lines 13-17, Applicant states

An adjuvant like an aluminum salt may activate macrophages causing increased risk of type I diabetes mellitus and other chronic immune mediated diseases. Using a non living vaccine that lacks an aluminum based adjuvant may decrease this effect.

It would be evident to the skilled worker that the replacement adjuvant should be at least as effective as the Al salt it replaces.

6. Enablement

Enablement issues were discussed in great detail in section 8-12 (pp. 24-55) of Applicant's Brief, which is incorporated by reference.

6.1. The new rejection relies heavily on Pediatric Infectious Diseases Journal, 18:217-22 (1999) ("PIDJ"). This

article must be placed in context.

The PIDJ article reports on an "Institute for Vaccine Safety" workshop. The Institute for Vaccine Safety is directed by Dr. Neal Halsey. According to Exhibit A2 (Nicholas Regush, "ABC News-Round Three: The Vaccine Machine, dated Thursday, August 19, 1999), the Institute receives funds from Merck, SmithKline Beecham, North American Vaccines, Connaught/Pasteur merieux and Wyeth-Lederle. Thus, it has a vested interest in allaying public concerns that immunizations could increase the incidence of diabetes. The IVS' conflicts of interest are commented on in Exhibit M1B (House of Rep. Majority Staff Report on Conflicts of Interest in Vaccine Policy Making, August 21, 2000); see also exhibit M1 (Opening Statement by Committee Chair Dan Burton, June 15, 2000).

Attendance at the Workshop was by invitation from Dr. Halsey only. While Dr. Classen was invited, none of the other researchers recommended by Dr. Classen were. However, the participants included representatives of Merck (Brunskill and Sharrar), Smith Kline (Hone), North American Vaccines (Keith), Wyeth Lederle (Paradiso), and Pasteur (Rubin).

Dr. Classen reviewed the PIDJ article in manuscript form and commented upon it, see Exhibit E2 (Classen letter of April 27, 1998 to Dr. Halsey). The Examiner will note that he points out that there was no consensus reached and that it was misleading for Halsey (the author) to suggest otherwise.

We turn now to the specific teachings of the PIDJ article. This says, "no vaccines have been shown to increase the risk of type 1 diabetes in humans". Even if this statement were taken at face value, it does not address the utility standard under the patent law. The question is where the asserted utility is "credible", not whether it has been proven.

When draft utility Guidelines were introduced in 1994, Commissioner Lehman commented

The guidelines emphasize that any credible statement of utility consistent with the scope of the claimed invention that is made by an applicant will satisfy §101. In other words, if an applicant presents a scientifically plausible use for the claimed invention, it will be sufficient to satisfy the utility requirement. [emphasis added]

Consistently, the current March 1, 2000 Training Materials comment

An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the applicant to support the assertion of utility.

In reviewing the evidence adduced by PIDJ, it is important to keep in mind that Dr. Classen teaches that the incidence of diabetes is affected by the timing of immunization: beginning immunization early reduces incidence, while starting it late increases incidence. Thus, a study that merely looks at the effect of giving a particular immunogen on diabetes, and ignores the timing of the immunization, may overlook a real connection, especially if there was substantial variation in timing from subject to subject within the immunized group.

Reviewing the PIDJ article more closely, it attacks Applicant's epidemiological analysis on several grounds.

BCG/Moulton (unpublished)

With regard to applicant's peer-reviewed BCG data, it concedes (based on an unpublished review by Dr. Moulton) that the rate of diabetes type 1 "in countries where BCG is routinely given at birth or at 1 to 3 months of age are generally lower

than the rates where BCG is not given or given at >1 year of age". (219 col. 1). However, PIDJ suggests that the according to "preliminary data" from a "multiple regression analysis"¹ differences "decrease" after "adjustment for distance from the equator, per capita gross national product, child mortality and per capita caloric intake". See also page 218, speculating that cold stress increases incidence rates. PIDJ also intimates that "several other factors" could explain the observed differences in diabetes incidence, including "genetic differences in populations and increased exposure to immune modulating infections early in life in tropical climates". (page 219).

Looking at Applicant's data (Appl., page 101), it is striking that Iceland (pertussis, no BCG) had a lower incidence (10.8) than the less northerly, equally developed, equally Caucasian study populations of England (16.4), Northern Ireland (16.6), Scotland (19.8), Denmark (21.5), Norway (20.8), and Finland (42.9) (late immunizations). Moreover, among Southern European states, Italy (6.8, 6.5, 30.2²); no pertussis or BCG, France (7.8; pertussis BCG <2 mo) and Portugal (7.5; same) scored lower than Spain (10.6, 10.9; pertussis, no BCG). It should be noted that the countries of Western Europe have relatively high and similar per capita GNP.

Besides relying on Moulton's "analysis", the PIDJ article also cites a case-control study of BCG vaccination in Canada (Parent, 1997), the Chinese experience as reported by LaPorte, and the BCG component of the Blom (1991) study in Sweden.

The Canadian paper is discussed on page 49 of Applicant's

¹ It is not clear if this was Moulton's analysis, or Halsey's analysis of Moulton's data. Either way, the data is "preliminary" and unpublished, hence it has not yet passed peer review.

² The very high incidence of diabetes in Sardinian Italy can be explained on a genetic basis, see your spec., page 92, lines 18-27.

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June 2000 "Scientific Evidence" monograph, copy enclosed. Blom (cited as Bloom) is discussed on page 47, mostly in connection with MMR.

BCG/Parent (1997)/Canada

The Canadian study reported that the difference in mean age of diabetes onset between the BCG cases (11.8 years) and the unvaccinated cases (12.3 years) was not statistically significant. However this finding was reached after lumping together the cases receiving BCG at different ages.

In Parent (1997) table 4, BCG vaccination among children in case-control series B, Montreal, 1982-1986, 14 out of 249 (5.6%) diabetics had received BCG immunization after one year, versus 12 of 431 (2.8%) controls. This is an odds ratio of 2:1; the calculated relative risk would be 1.5:1 (95% confidence band of 1.03 to 2.17; see Classen, "Scientific Evidence", page 30 and Fig. 4D; Classen, Drug Safety, 21(5):423-5 (1999)). Thus, Parent (1997) table 4 is actually supportive of the hypothesis that the timing of BCG immunization affects diabetes incidence.

If, as asserted at Parent (1997), page 769, col. 2, and page 770, col. 1, most vaccines received BCG at birth, then the fact that mean age at diagnosis was very significantly ($P < 0.001$) higher among vaccinated (12.2 years) than nonvaccinated (9.2 years) IDDM cases suggests that early vaccination with BCG in fact retarded the onset of diabetes.

The Examiner's attention is respectfully directed to the discussion of Danish data at pp. 30-31 of Classen, "Scientific Evidence".

BCG/LaPorte/China

The LaPorte data from China (page 219, full para. 1) was reported at the IVS workshop but has not been published in a peer-reviewed journal. LaPorte apparently said that there is

marked variability in the incidence of type 1 diabetes within China even though BCG is given to almost all infants at birth.

The nature of this "variability" is not clarified; is it geographic or temporal? If temporal, were there any changes in what other immunogens were administered over the course of time? What about changes in caloric intake? If geographic, are there province-to-province differences in diabetes susceptibility among unvaccinated individuals? Did LaPorte control for the latitudinal factor suggested earlier in PIDJ?

If the Examiner wishes to rely on this aspect of the PIDJ disclosure, it is incumbent on the PTO to provide more specifics so that a rational analysis of the validity of LaPorte's data and methodology can be performed.

Various antigens/Blom study/Sweden

The Blom (1991) study in Sweden is cited by PIDJ in connection with the effect of measles, mumps, rubella, BCG, smallpox, tetanus, and pertussis immunization on the incidence of diabetes. Blom concluded that measles had a protective effect and that the other immunogens had not effect.

Blom's methodology is critiqued by the Classen "Scientific Evidence" monograph, page 47.

Pertussis

In the patent application, table I addressed pertussis as well as BCG. Classen table III also addressed pertussis in Pennsylvania. (changes in 1974 and 1983). The only discussion of pertussis in PIDJ is in connection with the "study in Sweden" (i.e., Blom, 1991) (page 219 col. 2), which has the weakness noted in the monograph.

HIB/Classen/Finland; Allegheny County

Appl. Table II studied the effect of several vaccination

programs in Finland (a clinical trial with Hib and meningococci polysaccharide in November 1974; a more antigenic pertussis vaccine in 1976; addition of MMR in 1982; a Hib conjugate trial in 1986; an addition of Hib in January, 1988). PIDJ only comments directly on your analysis of "unpublished data from a trial in Finland" of a Hib vaccination program.³

The PIDJ article declares that applicant's "analytic methods" were "incorrect" (page 219, col. 2, last full para.), but not why. Hence, its assertion is not entitled to any weight. Moreover, the PIDJ article does not look at the any of Applicant's other Hib/Finland data per Appl. Table II, or at Appl. Table III, showing a diabetes epidemic in 1985-89 in Allegheny County, Pennsylvania that applicant explains by reference to the addition of Hib to the schedule.

MMR

With regard to MMR, Classen Table III presents data from Finland. PIDJ just cites Blom (1991), who reported that measles vaccination in Sweden was protective against diabetes, and that rubella and mumps had no effect. Nonetheless, at page 218, col. 2, PIDJ admits that there is a high rate "of autoimmune type 1 diabetes mellitus in children with congenital rubella syndrome".

Smallpox

With regard to smallpox, Applicant presents epidemiological data from Denmark (Appl. Table IV), and discuss more generally

³ The trial in question is apparently the 1985-87 Eskola (1990) trial discussed in Classen (1997). However, Classen's monograph says that this study was (A) one dose at 24 mo or (B) 4 doses starting at 3 mo. PIDJ says that it was (A) one dose at 14 mo, or (B) doses at 3, 4 and 14 mos. We have checked the Eskola article and "24" was correct.

data from Netherlands⁴. PIDJ just refers to Blom (1991) vis-a-vis smallpox.

Miscellaneous

Besides these direct attacks, the PIDJ article also cited other allegedly "negative" epidemiological data on vaccines: (1) incidence of diabetes increased globally without new vaccines introduced (pp. 219-220, citing LaPorta); (2) Graves' prospective cohort study on effect of polio, DTP, Hib, MMR and HBV (page 220, col. 1); and (3) Willis (1997) study on HBV vaccination in New Zealand.

LaPorta's global analysis ignores Classen's clear teaching that it is not whether a vaccine is new or old, but when it is administered, that is relevant to the incidence of diabetes. A new vaccine administered at birth could decrease incidence; shifting and old vaccine from birth to three months could increase incidence.

Graves' data has been published (Ref. 5E; Diabetes care 22:1694-97, 1999). Classen's detailed critique has also been published. (Classen, Diabetes Care, 23:872, 1999.) In essence, it says that Graves' study group was too small, their follow-up too short, and their marker (an antibody) too nonspecific, since most people with a single auto antibody do not develop diabetes.

Turning to Willis' study on HBV vaccination in New Zealand, (Ref. 5F), this vaccine has been administered to newborn babies since February 29, 1998. Willis assumes that babies born before that date were not immunized with HBV at all. However, there was a "catch-up program"; only children older than 18 in 1988, i.e., those born before around 1970, were not offered the vaccine.

The PIDJ article cited (page 219, col. 2) your experimental studies of DTP immunization in mice. It commented that the

⁴ Published in Classen, Autoimmunity, 31:43-45 (1999).

cumulative incidence in DTP animals was "about 75%, similar to control animals in most other studies" and that the incidence of diabetes in your control animals was lower (about 25%) than expected.

One of Classen's control groups had a low incidence of diabetes because the animals were vaccinated at birth, just like the treated group. It has been confirmed by Noel McClaren (SE) that immunization of NOD mice at birth can prevent the development of diabetes.

Other than this attack, PIDJ confines itself to the remark, "selective vaccines are protective against type diabetes in animals but the data in humans are inconclusive."

PIDJ concedes at page 219, col. 1, full para. 2 that administration of BCG vaccine to infant BB rats protects against development of diabetes mellitus, citing Qin and Singth, J. Autoimmun. 10:271-8 (1997).⁵ PIDJ further concedes that FCA (which contains killed Mycobacterium butyricum) is protective, citing an apparently unpublished report from Dr. Noel Maclaren (a participant in the workshop). And PIDJ admits that the Classen articles (corresponding closely to the present specification) demonstrated that immunization of NOD mice with "anthrax and possibly other vaccines"⁶ resulted in a reduced incidence of diabetes.

In view of the deficiencies of PIDJ, the Examiner has failed to establish either that the PTO should doubt the assertion that vaccines can protect against or increase the risk of diabetes at

⁵ The title of this article refers to NOD mice, not BB rats, according to citation 42 in PIDJ's references.

⁶ Despite the "possibly", the evidence for the other vaccines (pertussis, diphtheria and tetanus) was actually stronger than for anthrax, but these other vaccines are standard childhood vaccines and hence it is politically sensitive for IVS to acknowledge a linkage between them and diabetes, even a favorable one.

cell, or the assertion that it is proper to extrapolate from efficacy against type I diabetes in mice to efficacy against type I diabetes in humans.

6.2. The Examiner relies on Boumpas as evidence that the underlying pathogenesis of SLE is not fully known. Even if this is accurate, that does not mean that SLE cannot be treated by immunological means. It is certainly known that SLE is an immunological disorder.

Applicants have shown that in a recognized animal model of SLE, early immunization reduces the incidence of SLE (Example 5). This was accomplished even though the underlying pathogenesis of SLE in the animal model is not fully known, either.

Empirical treatments are just as patentable as treatments which are the product of some elegant and complete theory of pathogenesis. Absent substantial reason to doubt the reliability of the MRL/MpJ-lpr mouse model --and Boumpas does not express such doubts-- the empirical success in mice renders the proposed human utility believable.

See more generally the discussion in sections 11 and 12 of Applicant's Brief.

6.3. There are now a large number of reports indicating vaccines may cause chronic immune mediated disorders. The key diseases are listed below.

1. Asthma and Allergies and different vaccines
See **Ref. 1E**

2. Gulf War Syndrome and vaccines
See **Ref. 5G, 5G2**

3. Lyme vaccine and Autoimmunity
See **Ref. 1A**

4. Supporting human references on autoimmunity
See **Ref. 5H**

5. Supporting animal data on vaccines and diabetes
See **Ref. 5E**

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6. Supporting human data on vaccines and diabetes
See Classen monograph entitled "**Scientific Evidence Proving Vaccines Cause Type I, Insulin Dependent Diabetes**"

7. Hepatitis B virus
See Classen (2000) page 29, 42, but cp. 49-50

While there is certainly some controversy as to the precise role of immunogens in autoimmunity, the patent standard does not require that there be a consensus, merely that the disclosed use be scientifically plausible.

Respectfully submitted,

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Enclosures

-Classen, "Scientific Evidence Proving Vaccines Cause Type I, Insulin Dependent Diabetes (IDDM), Draft Document (June 2000)
-Classen, "Scientific Evidence Proving Vaccines Cause Auto immunity other than Insulin Dependent Diabetes" (June 2000)
-Exhibits A2, M1B, M1, E2, 1E, 5G, 1A, 5E, 5H, 5G2
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